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AstraZeneca AB  
 Global Intellectual Property Patents  
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Application No. 99 931 710.0-2103	Ref A1931-1P EP	Date 06.03.2003
Applicant AstraZeneca AB		

**Communication pursuant to Article 96(2) EPC**

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

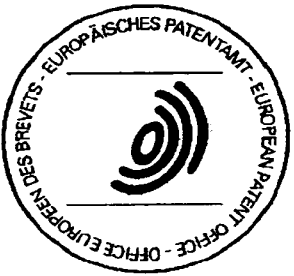
You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).



HERZOG A  
 Primary Examiner  
 for the Examining Division

Enclosure(s): 5 page/s reasons (Form 2906)

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Sheet 1  
FeuilleAnmelde-Nr.:  
Application No.: 99 931 710.0  
Demande n°:

The examination is being carried out on the following application documents:

Text for the Contracting States:

AT BE CH LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

Description, pages:

1-53 as originally filed

Claims, No.:

1-17 as received on 06.08.2002 with letter of 02.08.2002

The applicant introduced the following prior art documents:

D8: DE 19544687 A (disclaimer, cited by applicant)

D9: EP 0325397 A (disclaimer, cited by applicant)

The following documents are additionally introduced:

D10: CH 441366 A

D11: Tsuge, O. et al., Tetrahedron (1968), vol. 24, p. 2583-2590

D12: Ruggli, P. et al., Helv. Chim. Acta (1947), vol. 30, p. 1845-1852

D13: Hinsberg, K. et al., Biochem. Z., , 1937, vol. 289, p. 57-64

D14: Wieland, H. et al., Chem. Ber. (1931), vol. 64, p. 2513-2516

D15: Weinstock, L.T. et al., J. Med. Chem. (1979), vol. 22, no. 5, p. 594-597

D16: Nishizawa, S. et al., Tetrahedron Lett. (1995), vol. 36, no. 36, p. 6483-6486

D17: Fan, E. et al., J. Am. Chem. Soc. (1993), vol. 115, no. 1, p. 369-370

D18: Leung, M.-K. et al., J. Org. Chem. (1996), vol. 61, no. 12, p. 4175-4179

A copy of these documents is appended hereto.

The applicant's attention is drawn to the fact that these documents are merely a small selection of the novelty-destroying documents that could be retrieved in the prior art.



1. The present application does not meet the requirements of Article 52 EPC because the subject-matter of present claims 1 and 2 is not new in the sense of Article 54(1) and (2) EPC.

In addition to the compounds disclosed in D8 and D9 (introduced by the applicant), the following compounds in the prior art documents D10-D18 fall within the scope of present claim 1 and/or 2:

D10 discloses the compounds "1-Methyl-2-[4-(4-methyl-allophanoyl)-benzyl]-hydrazin", "1-Methyl-2-(4'-allophanoyl-benzyl)-hydrazin" and "1-Methyl-2-[4'-(4"-butyl-allophanoyl)-benzyl]-hydrazin" (cf. D10, col. 22-23, Beispiel 34).

D11 discloses acylurea derivatives of formula (V) (cf. D11, page 2585, Table 1, Examples 4, 5 and 6).

D12 discloses the compound "m-Xylylen-di-hamstoff" (cf. D12, page 1849, § 2).

D13 discloses "Kryogenin" (cf. D13, page 60, reaction scheme, product).

D14 discloses the compound "m-Phenylen-4.4'-disemicarbazid" (cf. D14, page 2515, last paragraph).

In D15, the compound 6a falls within the scope of present claim 1 (cf. D15, page 595, formula 6a).

D16 discloses the bis-urea compound 1 (cf. D16, page 6483, formula 1., X=O).

D17 discloses the bis-urea compound 4 (cf. D17, page 369, col. 2, formula 4., X=O).

D18 discloses the bis-urea compounds 41 and 42 (cf. D18, page 4178, Table 3).

Most of the cited documents or compounds therein are novelty-destroying due to the definition of the variables m and n (integer of from 1-3) in the present application and due to the fact that according to present claim 1, "one or more of



the hydrogens in such an alkylene-chain may optionally be substituted by anyone of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or hydroxy; or one or more of the methylene groups may optionally be substituted by a heteroatom such as O, N or S".

It is additionally mentioned that the expression "substituted" is not clear in this context since a hydrogen atom cannot be substituted (by substituents), but replaced only, whereas a methylene group could be **substituted**, i.e. carry substituents which replace one or two hydrogen atoms therein (-CH<sub>2</sub>- substituted by O might be -C(=O)- !), or **replaced**, i.e. a methylene group -CH<sub>2</sub>- is replaced by an oxygen atom -O-.

2. The examining division maintains the objection that the present application does not meet the requirements of Article 56 EPC over the whole scope of the claims since not all compounds falling within formula I in claim 1 are able to solve the problem posed.

With his letter of 02.08.2002, the applicant provided data (Appendix 4) showing the activity of some of the compounds in the present specification. In appendices 1-3, activity data for compounds exemplified in co-pending applications are provided. In appendix 5, additional data for compounds covered by co-pending applications which are not specifically exemplified therein are provided.

However, the additional data render it even more evident that the compounds which act as selective opioid  $\delta$  ligands and thus are able to solve the problem posed must have a very distinct structure.

It is also clear from the teaching of Takemori and Portoghese (Ann. Rev. Pharmacol. Tox., Vol. 32 (1992), p. 239-269; cited by the applicant on page 1 of the present specification) that a  $\delta$  opioid antagonist must have very distinct key recognition elements (message-address concept) to act as a  $\delta$  address mimic (cf. pages 250-256, especially page 254, Figure 9 therein).

All the examples in the present specification as well as all the compounds in the co-pending applications and given in the appendices 1-5 (provided by the applicant with his letter of 02.08.2002) share the structure element **N-CH<sub>2</sub>-(cyclohexyl or phenyl)-CH<sub>2</sub>-N**, i.e. the variables **n** and **m** in present formula I are **1**, and the methylene groups connected to the phenyl ring cannot be substituted.



The structure of the residue  $R^3$  also appears to be very important and is always either **cyclohexylmethyl-** or (optionally Y-substituted) **phenylmethyl-**.

The variable  $R^1$  is always either H or alkyl, and  $R^2$  represents alkyl or (optionally Y-substituted) phenyl. The variables  $R^4$  and  $R^5$  are as defined in present claim 3.

Should the applicant refuse to restrict the scope of present claim 1 accordingly, the application will be refused under Article 97(1) EPC.

Reference is made to the Decisions T409/91 (cf. Reasons for the Decision, especially paragraphs 3.3-3.5) and T939/92 (cf. Reasons for the Decision, especially paragraphs 2.4-2.6).

3. Irrespective of the above, it is mentioned that in the definition of the variables  $R^3$ ,  $R^4$  and  $R^5$ , alternatives (iv), the expression "heteroaryl-( $C_5$ - $C_{10}$  alkyl), where the heteroaryl has from 5 to 10 atoms" is probably not correct since this means that a heteroaryl is connected to the nitrogen atom via an alkylene chain of at least 5 carbon atoms (Article 84 EPC). A comparison with the examples shows that this was probably not intended.  
In addition, the expression "and wherein the aryl and heteroaryl may optionally and independently be substituted by 1 or 2 substituents Y" are confusing as well since no aryl group is present in said heteroarylalkyl substituent (Article 84 EPC). This error appears also in the definition of the variable  $R^3$ , alternative (v);  $R^4$ , alternatives (v) and (vii);  $R^5$ , alternative (v); and  $R^7$ - $R^{11}$ , alternatives (d) and (e).
4. The amendment of the incorrect formulae in the definition of the variable Y in claim 1 cannot be considered an obvious correction since said amendment is not the only correction possible. The corresponding formulae in the description are not correct either. The amendments thus clearly do not meet the requirements of Article 123(2) EPC, and the incorrect formulae have to be deleted from the claims and the description.
5. Claims 11, 12 and 13 as well as claims 15 and 16 have been drafted as separate independent claims. Under Article 84 in combination with Rule 29(2) EPC an application may contain more than one independent claim in a particular category only if the subject matter claimed falls within one or more of the exceptional



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Application No.: 99 931 710.0  
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situations set out in paragraphs (a), (b) or (c) of Rule 29(2) EPC. This is not the case in the present application.